Engineered Neural Networks using Microfabricated Cell Guidance Cues

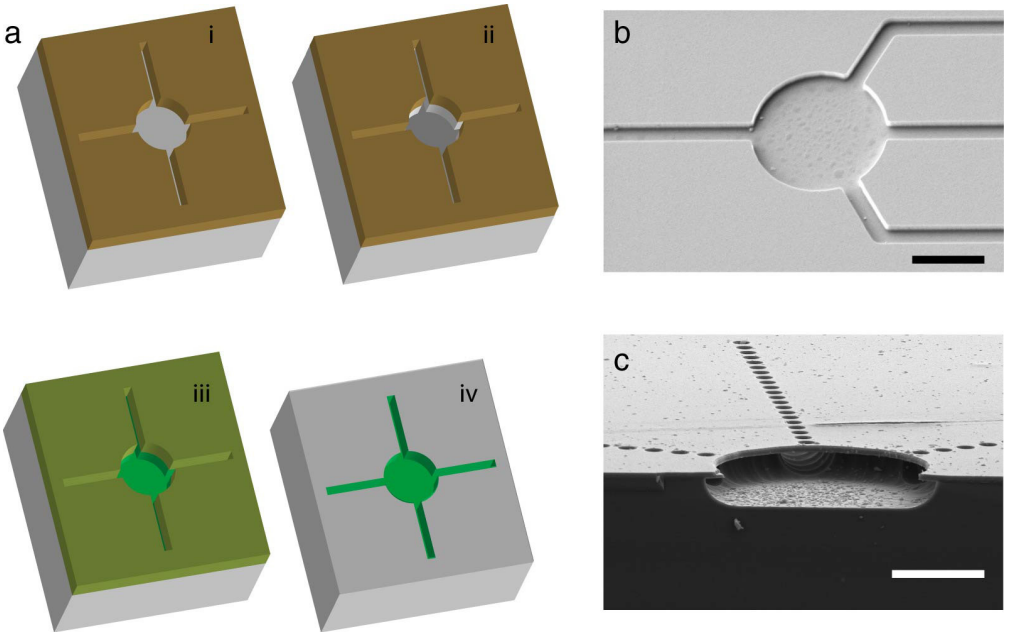

Figure 1: (a) Dual chemical and topographical guidance cue substrate preparation: (i) resist patterning, (ii) reactive ion etching of the glass substrate, (iii) adsorption of adhesive molecules, and (iv) acetone liftoff to remove the resist. (b) Reactive ion etched cell guidance cues. (c) Wet hydrogen fluoride etched buried guidance cues. Scale bars=10 µm.

Precise organization of neurons will ultimately help the understanding of brain function

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In order to test hypotheses regarding the relationship between brain network architecture and function, researchers require the ability to engineer, measure, and modify living neural networks in controlled environmental conditions. Eventually, such technology could provide the capability to repair damaged nerve tissue and fully restore lost motor, sensory, and cognitive functions. However, current neural engineering efforts organize large populations of neurons into grossly-defined patterns with minimal success at organizing individual synaptic connections (Reference 1). These connections are the key element of circuit connectivity and functionality, thus the objective here is to develop microfabrication methods for precisely organizing neurons into functional networks.

Specifically, Sandia is interested in monitoring the development of long-term potentiation (LTP) and long-term depression (LTD) in engineered networks of rat neurons. LTP and LTD are phenomena whereby stimulated neurons maintain a change in their electrical output after the cessation of stimulation, and these mechanisms are believed to underlie memory and learning *in vivo*. The synaptic interface between neurons will be controlled and varied with microfabricated cell guidance cues (Reference 2) in order to determine the influence of network architecture on the development of LTP and LTD. These cues contain patterned chemical and topographical features that promote neuron attachment (e.g., chemically via the charged amino acid poly-lysine) and outgrowth at pre-defined locations. Fabrication of these devices is shown in Figure 1. A working example is shown in Figure 2, where simple changes in guidance cue geometry controls the polarity of neurons. Figure 2c shows that optimized geometry of the guidance cues can be used

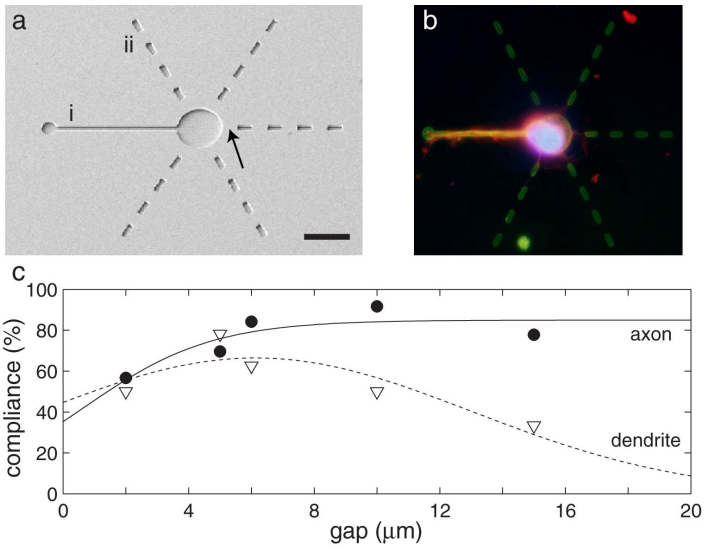

Figure 2: (a) Guidance cues for controlled neuron polarization. Continuous features (i) for directing axons and interrupted features (ii) for guiding dendrites are shown. (b) Fluorescence image of a properly polarized rat neuron. (c) Compliance of axons and dendrites as a function of the gap (arrow in a) between the node and the first interrupted feature.

to promote rapid neuron growth in one direction, which leads to axon development (electrical output), and to delay growth in other directions, which leads to dendrite development (electrical input).

Patch clamp and field recording electrophysiology are being used to measure the electrical response of engineered networks of neurons (Figure 3a). This system is capable of measuring microvolt changes in cell membrane potential, and, in conjunction with fluorescence probes, can be used to monitor coordinated activity such as calcium ion flow and action potential signaling. The experimental data is then used to train a computational model implemented in Sandia's custom circuit simulator program Xyce in order to predict network architectures that exhibit designed input/output characteristics. The ultimate objective is to decipher the mechanisms involved in human decision making, and to specifically understand the importance of the brain's corticostriatal networks in such cognitive processes. These networks integrate multiple sets of information (motor, sensory, cognitive, and reward); thus Sandia is constructing engineered corticostriatal networks and comparing the development of LTD/LTP in engineered networks to that measured in intact brain slices (Figure 3b).

Although just beginning, this work has resulted in additional projects. One is in collaboration with the University of Texas to study the repair of neuro-muscular junctions using neural engineering technologies. In another, funds from the Defense Advanced Research Projects Agency are being used to develop these microsystem techniques to engineer the hippocampal network, a region of the brain heavily involved in memory and learning.

References:

1. James, C.D, et al., IEEE Trans. Biomed. Eng. 2004; **51**, pp. 1640-1648.
2. Withers, G.S., James, C.D., et al., J. Neurobiology 2006; **66**, pp. 1183-1194.

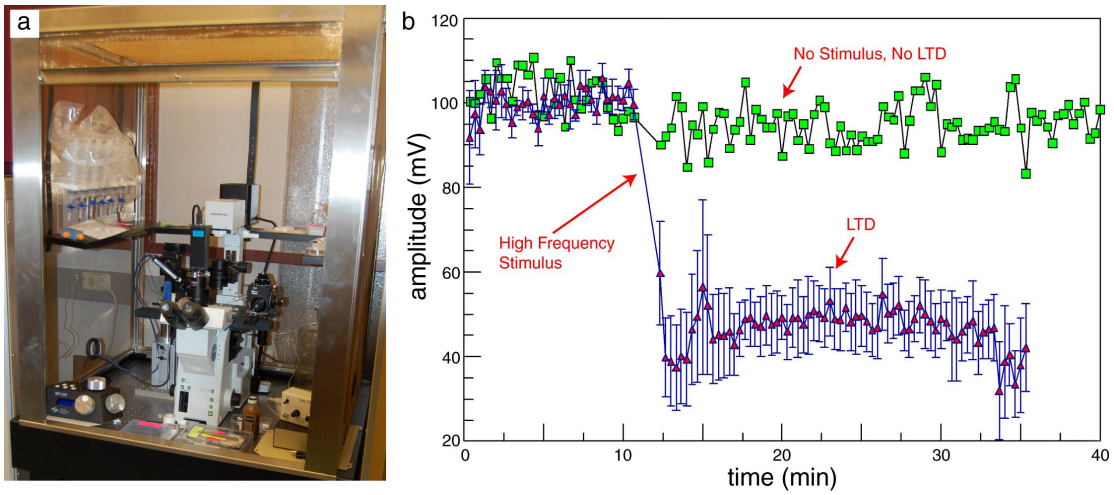

Figure 3: (a) Electrophysiology apparatus for monitoring electrical activity in living neural networks. (b) High-frequency stimulation-induced long-term depression measured in corticostriatal networks in a rat brain slice.

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